Mass Spectrometry in Medicinal Chemistry: Applications in Drug Discovery (Methods and Principles in Medicinal Chemistry), Volume 36

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The goal of *Mass Spectrometry in Medicinal Chemistry: Applications in Drug Discovery* is to describe the intimate relationship between bioanalytical mass spectrometry (MS) and the drug discovery process. The authors have assembled a fine collection that I thoroughly enjoyed reading.

The book is part of the series in Methods and Principles in Medicinal Chemistry from Wiley-VCH, edited by Raimund Mannhold, Hugo Kubinyi, and Gerd Folkers. As the editors point out, the importance of mass spectrometry in the drug discovery arena has been "largely unperceived" by medicinal chemists over the last twenty or so years. The collection of articles covers lead discovery and optimization using modern applications of mass spectrometry, reflecting the very real impact this technology has brought to bear on the central function of drug discovery. The book itself is edited by Klaus Wanner and Georg Höfner of the Center of Drug Research at the Ludwig-Maximilians-University in Munich. Both are actively engaged in research, most recently focusing on compounds that target neurotransmitter receptors, and they have been leading proponents of mass spectrometry in medicinal chemistry for several years.

Although a quick search of amazon.com reveals several thousand titles focused on medicinal chemistry, less than a handful discuss the application of mass spectrometry in this arena. There are so many applications of mass spectrometry in biological chemistry that it will be most useful for medicinal chemists to have their own dedicated collection of articles assembled here in *Mass Spectrometry in Medicinal Chemistry*.

The book is organized into thirteen chapters with the first providing an introduction and subsequent chapters detailing specific applications in use today as part of the drug discovery effort, subdivided into four subheadings; studying target–ligand interactions by analyzing the ligand alone, by analyzing target–ligand complexes, or by studying the target-binding site by MS, as well as a final chapter dealing with MS in early pharmacokinetics.

Chapter 1 ("Mass Spectrometry in Bioanalysis: Methods, Principles and Instrumentation") is necessarily brief and covers the basics of MS as it relates to analysis of biomolecules. The text reads well and is generally consistent with the msterms.com list of definitions, bringing me to my only significant criticism. The opening paragraph of the fundamentals section has the potential to confuse, as a result of the need to accurately educate the reader while avoiding lengthy explanation. This is a minor point and the text moves nicely through ionization, mass analyzers, and detectors and then ends up with brief descriptions of quantitative analysis, drug metabolism, and protein/peptide analysis, providing a necessary introduction for the coming chapters.

The "meat" of this tome is found in section II with seven substantial chapters on "studying target–ligand interactions analyzing the ligand by MS" covering the major methodologies used by the pharmaceutical industry for high-throughput screening. Marshall Siegel from Wyeth Research describes the theory and practice of "Drug Screening Using Gel Permeation Chromatography Spin Columns Coupled with ESI-MS." Molecules that bind a target protein are swept through the column rapidly, whereas those that do not are retained. Both theory and practical details are covered, and there are many illustrations of relevant examples throughout. The chapter that follows by Allen Annis, Cheng-Chi Chuang, and Naim Nazef at Schering-Plough describes "ALIS: An Affinity Selection–Mass Spectrometry System for the Discovery and Characterization of Protein–Ligand Interactions." Rapid size-exclusion chromatography is used to separate ligand–protein complexes, as described in the previous chapter, with a downstream reverse-phase chromatography step to separate the ligand from the protein. There is again consideration of theory, and many examples are used to illustrate the versatility of the system.

In chapter 4, Timothy Cloutier and Kenneth Comess at Abbott Labs describe "Library Screening Using Ultrafilitration and Mass Spectrometry." The approach is similar to that described in the previous two chapters with the major difference that ultrafiltration is used to separate the protein-bound ligand from the unbound ligand. This is a shorter chapter that focuses on the practical experiences of the authors and nicely complements the preceding chapters.

Chapter 5 is written by Hubertus Irth at Vrije Universiteit Amsterdam and describes "Continuous-flow

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Systems for Ligand Binding and Enzyme Inhibition Assays Based on Mass Spectrometry." Mass spectrometry is used to monitor substrate and product concentrations from an enzyme reactor such that introduction of an inhibitor results in perturbation of these signals. The complexity of the setup is offset by the advantage that actual inhibition of function is measured in distinction to simple binding.

Chapter 6 is by David Schreimer and colleagues at the University of Calgary and describes "Frontal Affinity Chromatography—Mass Spectrometry for Ligand Discovery and Characterization." I have always found FAC-MS particularly elegant after hearing about it from David at one of the ASMS Asilomar meetings. Mass spectrometry is used to monitor the appearance of freshly introduced small molecules as they flow through a column of immobilized receptor with the appearance of ligand molecules delayed as they partition to an immobile bound state. The chapter is very well written and explains the exact place for FAC-MS in the drug discovery field, able to cope with quite complex mixtures of poorly defined molecules such as natural product extracts.

Chapter 7 is contributed by the editors and describes the use of "MS Binding Assays—An Alternative to Radioligand Binding." Quantitative mass spectrometry is used to measure either unbound or bound ligands after incubation with a receptor. The chapter is very clear and well illustrated with many examples from the neurotransmitter receptor field.

The final chapter (8) of this section written by Martin Vogel, Andy Scheffer, Andre Liesener, and Uwe Karst describes "Laser Desorption Assays–MALDI-MS, DIOS-MS and SAMDI-MS." Although the rest of this section focused on applications of ESI-MS, this one covers laser desorption techniques that are in their infancy in this analytical realm. The authors do a concise job of describing progress and illustrating potential for the future.

Section III of the book has two chapters describing direct analysis of target–ligand complexes by mass spectrometry. The first of these written by Mark Cancilla and Daniel Erlanson of Sunesis Pharmaceuticals and describes "Tethering: Fragment-based Drug Discovery by Mass Spectrometry." This approach was developed because of the difficulties in detecting low-affinity binding to targets; an engineered tether is used covalently link the target to the ligand upon weak binding for downstream identification by mass spectrometry. The Sunesis strategy is described concisely.

In the next chapter (10) Steven Hofstadler and Kristin Sannes-Lowery of Isis Pharmaceuticals describe "Interrogation of Noncovalent Complexes by ESI-MS: A Powerful Platform for High Throughput Drug Discovery." This is a relatively brief but enjoyable account of the authors' considerable experience performing ESI-MS under non-denaturing conditions that retain structure and non-covalent binding of ligands.

Section IV of the book again has two chapters, this time describing how protein hydrogen/deuterium exchange measurements (HDX) can be used to study target-binding sites. First, Mei Zhu, David Hambley, and Michael Gross of Washington University describe "Quantification of Protein–Ligand Interactions in Solution by Hydrogen/Deuterium Exchange (PLIMSTEX)." The chapter also includes a section on fast radical-footprinting for protein–ligand interaction analysis (FPOP)—a technique that is poised to deliver important and complementary insights into the protein–ligand interaction.

Second, Yoshitomo Hamuro, Stephen Coales, and Virgil Woods of UCSD describe "Protein-targeting Drug Discovery Guided by Hydrogen/Deuterium Exhange Mass Spectrometry (DXMS)." This chapter gives a concise overview of the contribution HDX measurements can make to the drug discovery process and a thorough introduction to the work in this area at UCSD. The two chapters combined make for very thorough coverage of HDX mass spectrometry and its role in studying protein–ligand interactions.

The final section of the book on "Mass Spectrometry in Early Pharmacokinetic Investigations" has a single chapter written by Walter Korfmacher at Schering-Plough. This chapter rounds out the book nicely, highlighting the role of mass spectrometry in events after a lead is identified toward the definition of a new chemical entity that will move successfully through clinical trials.

Overall, *Mass Spectrometry in Medicinal Chemistry* is an excellent choice not only for young scientists entering the drug discovery field, but also for established mass spectrometrists interested in understanding applications that are developing in diverse fields. From a personal perspective, I found nearly all of the chapters especially illuminating because of their focus on the high-throughput needs of the field. Hopefully, this underlying theme will help to educate readers as to how basic technology gets driven in exciting yet somewhat unpredictable directions by commercial forces. Despite being priced a little on the high side ($200 US), I believe *Mass Spectrometry in Medicinal Chemistry* is still an excellent value and should be required reading, particularly for the growing population of young scientists joining the field of mass spectrometry.